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EXAMINER	
WEHBE, ANNE MARIE SABRINA	
ART UNIT	**PAPER NUMBER**
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/903,327	Applicant(s) Nemerow
	Examiner Anne Marie Wehbé	Art Unit 1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Feb 3, 2003* .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-27, 29-34, and 36-39* is/are pending in the application.

4a) Of the above, claim(s) *38 and 39* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-27, 29-34, 36, and 37* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicant's amendment and response to the Restriction Requirement received on 3/26/03 has been entered. As requested, claims 28 and 35 have been canceled and claim 34 has been amended. Claims 1-27, 29-34, and 36-39 are pending in the instant application. Of these, claims 38-39 have been withdrawn as being drawn to subject matter non-elected with traverse in paper no. 19. Claims 1-27, 29-34, and 36-37 are currently under examination. An action on the merits follows.

Restriction/Election

Applicant's election with traverse of the subject matter of group I is acknowledged. The applicant's have traversed the grounds for restriction between Groups I and III on the grounds that the bifunctional molecule of Group I is a subcombination of the targeted delivery vectors of Group III. In view of applicant's arguments, claims 29-34 and 36-37 are hereby rejoined with the subject matter of Group I. However, claims 38-39 are not directed to compositions comprising either the subcombination or the combination recited in claims 1-27, 29-34, and 36-37. Claims 38-39 are drawn to methods of targeted gene therapy using the combination of claim 36 or 37. The previous office action clearly stated that the bifunctional molecules of the instant invention can be used for substantially different methods than targeted gene therapy, such as for *in vitro* binding assays. Please note that MPEP 806.05(h) states that it is proper to restrict between a product and

a process of using the product if **either** or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product **or (2) the product as claimed can be used in a materially different process of using that product**. The applicant has not provided any arguments traversing this grounds for restriction. Therefore, the restriction requirement between claims 38-39 and the remaining claims is still deemed proper and is made FINAL.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 6 and 13-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 6 is indefinite in the recitation of "the linker". Claim 6 depends on claim 2. Claim 2 does not provide antecedent basis for the recitation of "the linker" in claim 6.

Claims 13-14 are indefinite in the recitation of a nucleic acid encoding an antibody portion. Claim 13 depends on claim 10 which depends on claim 1. Claim 14 depends on claim 11 which ultimately depends on claim 1. Claim 1 recites a bifunctional molecule which comprises an antibody protein. None of claims 1, 10, or 11 provide antecedent basis for a nucleic acid encoding an antibody portion. Further, claims 10 and 11 are directed to antibody proteins with specific amino acid sequences. Therefore, the recitation of nucleic acid sequences in claims 13 and 14 is confusing in that it is unclear whether the applicant intends to claim the bifunctional molecule which comprises an antibody protein or nucleic acid sequences which encode the antibody. The applicant is reminded that subject matter drawn to nucleic acid sequences is non-elected in the instant application. Alternatively, it is unclear whether the applicant intended a product by process claim, wherein the antibody portion of the bifunctional molecule is produced from the recited nucleic acid sequences. Clarification regarding the intended invention in claims 13 and 14 is requested.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) The invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-9, 12, 15-27, 29-34, and 36-37 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 98/40508 (9/17/98), hereafter referred to as Sosnowski et al. The applicant claims a bifunctional molecule comprising an antibody-binding portion which binds to a viral protein that binds to a_v integrin and a targeting agent which binds to a cell surface protein that activates the phosphatidylinositol 3 (PI3K) signaling pathway. The applicant further claims said bifunctional molecule wherein the antibody binding protein binds to the penton base of an adenovirus capsid protein or to a protein which includes an RGD motif, or wherein the targeting agent is an FGF or EGF or an agent which binds to the EGF or FGF receptors. In addition the applicant claims said molecules wherein the antibody is a Fab'2 or Fab fragment, wherein the molecule comprises a fusion protein or chemically conjugated polypeptides, or wherein the molecule further comprises a peptide linker that links the antibody to the targeting agent. The applicant also claims a combination of the bifunctional molecule and an adenovirus vector which encodes a therapeutic protein.

Sosnowski et al. teaches retargeted, tropism modified viral vectors, particularly adenoviral vectors encoding a therapeutic gene which are complexed with a molecule that comprises a antibody which binds to a component of the viral capsid and a targeting antibody or protein which binds to receptors which are capable of internalization on target cells (Sosnowski et al., pages 4-5, and 171-174, claims 1-30). Examples of targeting proteins include FGF2, EGF,

PDGF, VEGF and cytokines (Sosnowski et al., pages 35-36). In particular, Sosnowski et al. teaches that the antibody can be conjugated to the targeting ligand, or alternatively that the antibody and targeting ligand are a fusion protein (Sosnowski et al., page 6, lines 23-27). Sosnowski et al. also teaches that the conjugate of antibody and ligand can include a peptide linker, and that the conjugate can be produced by chemical coupling methods or by recombinant expression of chimeric DNA molecules (Sosnowski et al., page 16, lines 26-30). Sosnowski et al. further teaches that the antibody which binds to the capsid can bind to the penton, which includes the penton base and penton fiber (Sosnowski et al., pages 23-24 and 27). In addition, Sosnowski et al. teaches that the antibody can be a Fab fragment or a single chain antibody (Sosnowski et al., pages 29-30). Finally, Sosnowski et al. teaches that the tropism modified viruses can target and be internalized by cells which express the binding partner of the targeting ligand (Sosnowski et al., see for example pages 107-108). Thus, by teaching all the limitations of the claims as written, Sosnowski et al. anticipates the instant invention as claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having

ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 10-11, and 13-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 98/40508 (9/17/98), hereafter referred to as Sosnowski et al., in view of Stewart et al. (1997) EMBO J., Vol. 16, No. 6, 1189-1198. The applicant claims a bifunctional molecule comprising an antibody-binding portion which binds to a viral protein that binds to α_v integrin and a targeting agent which binds to a cell surface protein that activates the phosphatidylinositol 3 (PI3K) signaling pathway. The applicant further claims said bifunctional molecule wherein the antibody binding protein binds to the penton base of an adenovirus capsid protein and wherein the amino acid sequence of the antibody comprises the amino acid sequence set forth in SEQ ID NOS. 2, 4, or 6 or a sufficient portion thereof for antigen recognition.

In regards to claims 13-14, the applicant claims bifunctional molecules comprising an antibody portion comprises the amino acid sequence set forth in SEQ ID NOS. 2, 4, or 6 or a sufficient portion thereof for antigen recognition, wherein the nucleic acid encoding the

antibody is selected from the coding portions of SEQ ID NOS 1, 3, or 5, sequences degenerate to SEQ ID NOS 1, 3, or 5 or sequences which hybridize under high stringency conditions to SEQ ID NOS 1, 3, or 5. As noted above in the rejection of claims 13-14 under 35 U.S.C. 112, second paragraph, the claims are confusing in that it is unclear whether the applicant is claiming the bifunctional antibody which is a protein or the nucleic acid sequences which encode the antibody portion of the bifunctional molecule. As noted above, subject matter drawn to nucleic acids has been non-elected in this application. Further it is unclear whether applicant intended to claims a product by process where the antibody is produced from the recited nucleic acid sequences. For the purposes of examining the claims in regards to prior art, the claims have been interpreted as being drawn to the bifunctional molecule which is an antibody conjugated to a targeting agent. Since the product is an antibody with a particular amino acid sequence, the exact sequence of a nucleic acid which may encode the recited amino acid sequences does not carry patentable weight as the product, for the purposes of patentability, is defined by its structure and properties and not on the process or reagents used to make the product. Case law states that "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985) (citations omitted).

Sosnowski et al. teaches retargeted, tropism modified viral vectors, particularly adenoviral vectors encoding a therapeutic gene which are complexed with a molecule that comprises a antibody which binds to a component of the viral capsid and a targeting antibody or protein which binds to receptors which are capable of internalization on target cells (Sosnowski et al., pages 4-5, and 171-174, claims 1-30). Examples of targeting proteins include FGF2, EGF, PDGF, VEGF and cytokines (Sosnowski et al., pages 35-36). In particular, Sosnowski et al. teaches that the antibody can be conjugated to the targeting ligand, or alternatively that the antibody and targeting ligand are a fusion protein (Sosnowski et al., page 6, lines 23-27). Sosnowski et al. also teaches that the conjugate of antibody and ligand can include a peptide linker, and that the conjugate can be produced by chemical coupling methods or by recombinant expression of chimeric DNA molecules (Sosnowski et al., page 16, lines 26-30). Sosnowski et al. further teaches that the antibody which binds to the capsid can bind to the penton, which includes the penton base and penton fiber (Sosnowski et al., pages 23-24 and 27). In addition, Sosnowski et al. teaches that the antibody can be a Fab fragment or a single chain antibody (Sosnowski et al., pages 29-30). Finally, Sosnowski et al. teaches that the tropism modified viruses can target and be internalized by cells which express the binding partner of the targeting ligand (Sosnowski et al., see for example pages 107-108).

Sosnowski et al. differs from the instant invention in that Sosnowski et al. does not teach the use of the DAV-1 antibody and the antibody which binds to the adenovirus capsid or penton. Please note that the specification discloses that the DAV-1 antibody comprises the

heavy and light chain amino acid sequences set forth in SEQ ID NOS: 2 and 4 and that SEQ ID NO: 6 is a portion of the heavy chain. Stewart et al. supplements Sosnowski et al. by teaching the DAV-1 antibody which binds to the penton base of adenovirus, specifically to the RGD containing motif IRGDTFATR (Stewart et al., pages 1189, and 1196). While Stewart et al. does not specifically disclose the amino acid sequences of the heavy and light chains of the full length DAV-1 antibody or the Fab fragment, the particular amino acid sequence of the DAV-1 antibody is intrinsic to the antibody itself, as the antibody is a protein which consists of amino acids.

As discussed above, Sosnowski et al. provides motivation for using antibodies against components of the adenovirus capsid including the penton in order to block the natural tropism of the adenovirus. Stewart et al. further provides motivation for using a fab fragment of the DAV-1 antibody by teaching that the penton base is critical in the cell entry of adenovirus and that the fab fragment of the DAV-1 antibody binds to all exposed RGD motifs, including mobile motifs, and completely blocks adenovirus infectivity (Stewart et al., page 1191, Figure 2b, and page 1194, column 2). Therefore, in view of the teachings of Soskowski et al. to use antibody against adenovirus capsid such as penton and penton base, and the motivation to use a Fab fragment of the DAV-1 antibody provided by Stewart et al., it would have been *prima facie* obvious to the skilled artisan at the time of filing to use the DAV-1 antibody as disclosed by Stewart et al. in the bifunctional molecules taught by Sosnowski et al. Further, based on the high degree of skill in molecular biology at the time of filing and the ability of the fab fragment

of DAV-1 to bind to mobile RGD motifs, the skilled artisan would have had a reasonable expectation of success in making a bifunctional molecule comprising the Fab fragment of DAV-1 and a targeting ligand such as FGF-2 capable of binding adenovirus and retargeting the virus to cells expressing the FGF receptor.

No claims are allowed.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (703) 306-9156. The examiner can be reached Mon-Fri from 10:30-7:00 EST. If the examiner is not available, the examiner's supervisor, Deborah Reynolds, can be reached at (703) 305-4051. General inquiries should be directed to the group receptionist whose phone number is (703) 308-0196. The technology center fax number is (703) 308-4242, the examiner's direct fax number is (703) 746-7024.

Dr. A.M.S. Wehbé

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER